I hereby certify that this correspondence is being deposited with the United States Postal Services on the date set forth below as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Date of Signature
and Deposit: _____ _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Duchesnay Inc.
Serial No.:	10/670,907
Filed:	September 25, 2003
Title:	METHOD OF PREPARING PHARMACEUTICAL DOSAGE FORMS CONTAINING MULTIPLE ACTIVE INGREDIENTS
Examiner:	Choi, Frank I.

DECLARATION UNDER 37 CFR 1.132

Dear Sir:

I, Victor H. Shulman, of the City of Thornhill, Ontario, Canada, being duly sworn, **MAKE OATH AND SAY AS FOLLOWS:**

1. This Declaration sets forth my opinion relating to this matter and the basis for my opinion.

I. **EXPERIENCE AND QUALIFICATIONS**

2. I am a pharmacist. I was educated and trained at the Witwatersrand School of Pharmacy, Johannesburg South Africa and also obtained a diploma in production management (with distinction) from Damelin Management College, Johannesburg South Africa. I am a registered Pharmaceutical Chemist and member of the Pharmaceutical Society of Great Britain.

3. I have now gained over 40 years of international experience in Pharmaceutics, including Good Manufacturing Practices (GMP) and industry compliance, both at brand names and generic pharmaceutical companies.

4. My projects have included, for example, redesigning of tooling engraving, implementation of aqueous ultrasonic cleaning, scale up, reformulation, SOP development, process validation, and process and efficiency improvement.

5. I also hold teaching roles. I am currently lecturing in Basic Pharmaceutics at Seneca College (School of Biological Sciences and Applied Chemistry) in both their postgraduate and continuing education courses. I am also currently training Health Canada (HPBFBI) inspectors in Basic Pharmaceutics through The Academy of Applied Pharmaceutical Sciences.

6. I am also working as an independent consultant and president of Darvic Consulting Inc. specializing in formulations: formulating capsules, tablets and coated tablets for the Pharmaceutical and Nutraceutical industries.

7. Throughout the years, I have developed strong practical "hands-on" experience in the field of roller compaction for dry granulations.

8. My curriculum vitae is attached as **Exhibit A** to my Declaration.

9. I am one of the inventors of the method for the preparation of pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine Succinate as described and claimed in United-States application No. 10/670,907.

10. I was asked to explain how we came to the presently claimed method, and more specifically to the use of roller compaction in the preparation of a dosage form comprising Pyridoxine HCl and Doxylamine succinate, an example of which is Diclectin™.

II. EFFORTS DEVELOPED TO OBTAIN UNIFORM DRY MIXING OF POWDERED PYRIDOXINE HYDROCHLORIDE AND DOXYLAMINE SUCCINATE

A) PREVIOUS DICLECTIN™ FORMULATION AND PROCESS

11. Diclectin™ was previously on the Canadian market as an enteric sugar coated tablet comprising 10 mg Pyridoxine HCl and 10 mg Doxylamine succinate.

12. Sugar Coated Diclectin™ was being manufactured using the method of dry blending and compression of the resultant blend.

13. At the time Diclectin™ was first developed, the requirements of Health Canada on the tablets mainly concerned the release of active ingredient(s), which had to be assayed on one of the actives, the results for the second one being assumed to be similar.

14. Additional testing on the sugar coated tablet showed that both active ingredients, namely Doxylamine Succinate and Pyridoxine HCl, generally met Canadian content uniformity requirements in the finished tablet. Content uniformity at the level of the initial blend of ingredients was not specifically considered at that time.

15. Content uniformity is generally defined as the quantity of active ingredient in a tablet (for example) compared to the stated quantity, generally expressed as a percent.

16. In the previous Diclectin™ manufacture process, we were using an overage of about 10% Pyridoxine HCl for several reasons.

17. We had observed a loss of this active ingredient during the manufacturing process in comparison to Doxylamine succinate, which we did not fully understand at that time, i.e. before we made the invention described and claimed in the application No. 10/670,907. We observed, for example, that Pyridoxine HCl would stick to the polyethylene bags lining the storage drums in which the raw materials or the blend of all Diclectin™ ingredients were kept before tabletting.

18. In addition, it was also a relatively standard practice at that time to include overages for vitamin compounds, most of them being known or believed to degrade over time in the finished tablet.

19. The use of a Pyridoxine HCl overage was however costly and did not always give consistent results in the finished tablets.

B) NEED FOR A NEW MANUFACTURING PROCESS

20. In about 2001-early 2002, we were in the process of modifying the Diclectin™ sugar enteric coating, eliminating lactose from the previous Diclectin™ formula and also aiming at a better formulated product throughout the manufacturing line.

21. In particular, we were aiming at a product acceptable to the Food and Drug Administration (FDA) that would be ultimately saleable in the USA.

22. Without going into detail, it seems useful to mention that to be acceptable to the FDA, all stages of a product manufacturing process, from blending to the final product, must meet the United States Pharmacopeia (USP) specifications for content uniformity and dissolution, which specifications are even tighter than those used for previous Diclectin™.

23. In particular, at that time the newly introduced FDA criteria required, for a product containing 2 active ingredients, to have content uniformity for both active ingredients with a relative standard deviation (RSD) of less than 5%. We thus aimed at conforming to the strictest possible guidelines with the new Diclectin™ process and formulation.

24. At first, the manufacturing method of previous Diclectin™ (dry blending and compression) was simply mimicked to produce the new formulation (i.e. without lactose, etc.) using the same class of Mixers and Tablet Compression machinery.

25. However, despite the use of varying blending times in the first step (dry blending),

the two actives (Doxylamine succinate and Pyridoxine HCl) would generally not produce an acceptable assay for Content Uniformity in the resulting blend.

26. Standard practice to obtain a uniform dry blend in such cases then was, and still is, to reduce the particle size of the actives to increase their surface area and thereby improve the mixing.

27. The original Diclectin™ formulation called for the Doxylamine succinate and Pyridoxine HCl to be passed through a #20 Mesh Screen.

28. We reduced the screen size to half, and tried to pass the Doxylamine succinate and Pyridoxine HCl through a #40 mesh screen – the Pyridoxine HCl passed through this smaller mesh but the Doxylamine Succinate "melted" and blocked the screen.

29. We increased the screen size to a #30 mesh screen and both the Doxylamine Succinate and Pyridoxine HCl passed through the mesh. We thus chose to try further with this screen.

30. We then proceeded to pass the Doxylamine Succinate and Pyridoxine HCl through a #30 mesh screen and tried mixing for various time periods to obtain blend uniformity.

31. Thus, quite surprisingly, the two powders of active ingredients, when dry blended, would not produce a uniform blend, whatever the method used and even when diluted with excipients.

32. In addition, on compressing the blend into cores, for use in later coating experiments, we found that analysis of the cores produced results that had content uniformity, with however a RSD around 8-12% (if I remember correctly), which was not within the newly required FDA specifications.

33. Thus, at least in view of obtaining fully acceptable content uniformity of the dry blend as well as the tablets, the manufacturing process had to be changed.

C) SEARCHING FOR THE CAUSE OF THE LACK OF UNIFORM DRY MIXING

34. From the knowledge we had on Doxylamine succinate and Pyridoxine HCl at that time, nothing explained why they would not uniformly mix. To the naked eye, the powders appear to be similar.

35. We first performed laser particle sizing of the Doxylamine succinate and Pyridoxine HCl, as well as of the final blend, which indicated that there were significant differences between the particle sizes of the Doxylamine succinate and those of Pyridoxine HCl.

36. However, the size of the particles itself does usually not permit to predict many of the properties of interest in pharmaceutical manufacturing, such as flow characteristics (including possible electrostatic activity), compressibility or segregation tendencies of the powders.

37. We then decided to look at the particles of the Doxylamine succinate and Pyridoxine HCl, as well as to the final blend, under an Electron Microscope to try and determine the cause(s) of the problem.

38. Only the results of this examination allowed us to assess the possible reasons for our previous failures in dry mixing.

D) ELECTRON MICROSCOPY RESULTS

1 - Doxylamine succinate

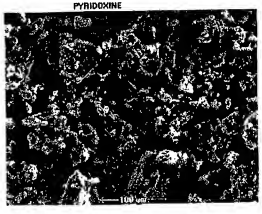
39. The Doxylamine particles appeared to be of larger size than those of Pyridoxine, with distinct Rod Shapes. The particles appeared smooth and looked waxy.

40. In bulk, the material had a damp appearance, with a tendency of clumping together.

41. The material would only pass through the minimum of a #30 Mesh Screen.

42. From the sizing of the particles and from the shape, they appeared completely unlike those of the Pyridoxine HCl.

2 - Pyridoxine hydrochloride



43. The Pyridoxine particles appeared to be of smaller size than those of Doxylamine, with a granular shape. The particles appeared irregular and angular.

44. In bulk, the material had the appearance of granular sugar and was free flowing.

45. The material passes through both a #40 and a #60 mesh screen. It also fractured easily through any size of mesh screen.

46. From the sizing of the particles and from the shape, they appeared completely unlike those of the Doxylamine Succinate.

3 – Technical reason for the two powders not producing a uniform blend

47. Only after microscopic examination of the two powdered materials, which is generally not done during the development of a manufacturing process since it is a tedious and expensive method, we could determine that at least one of the then unknown reasons why dry mixing did not result in a uniform blend was the very different microscopic structures of the active ingredient powders, namely a hard granular powder and a waxy powdered material.

48. We then had to explore answers as to how the manufacturing method could be altered to obtain a good mix producing consistent blend uniformity assays.

II. INTRODUCTION OF THE ROLLER COMPACTOR

49. The manufacturing method of dosage forms including Pyridoxine HCl and Doxylamine succinate as active ingredients including using a roller compactor is defined in the claims of the subject application.

50. When first introducing the roller compactor in the manufacturing process however, we used the same above-mentioned overage of about 10% for Pyridoxine HCl. Indeed, we were not expecting any change due to the introduction of the roller compactor with regard to the relative loss of this active ingredient during manufacturing.

51. We then observed that most content assays of the resulting tablets arrived at about 110% Pyridoxine HCl for about 100% Doxylamine succinate. There was therefore surprisingly no more loss of Pyridoxine HCl relative to Doxylamine succinate in the process comprising the use of a roller compactor. The new manufacturing method would unexpectedly allow for stopping the use of an overage of an active Ingredient relative to another to compensate for potential active ingredient loss.

52. In addition, passing a pre-mix[1] of the two actives with at least one excipient (thus, a non-uniform mix) into a roller compactor and breaking the resulting compacted product would unexpectedly result in granules meeting the FDA content uniformity requirements in terms of active ingredients (with a RSD of below about 4%).

53. I have to say that although I already knew the roller compaction technique well at that time, I could not have predicted that the content uniformity of the resulting granules would satisfy the strict FDA requirements.

54. In our testing, we mainly used a mesh size of 16 for sieving the broken compacted product, which is a mesh size suitable for further processing, namely the formation of unitary dosage forms, for example tabletting. A mesh size of 20, for example, would also be suitable. Smaller granules however, may result in more fines, which (although containing both active ingredients) would have to be discarded or recycled upstream in the process.

55. We went on to observe the structure of the roll compacted granules under an Electron Microscope:

56. The granules obtained after roller compaction of the two actives with at least one

[1] The pre-mix mentioned here is not considered a blending step in itself for the purpose of the FDA requirements. Thus the first stage in the process where content uniformity is requested, when using a roller compactor, would be the resulting granular blend.

excipient had a unique appearance, distinct from those of the above-described actives.

57. The roller compacted granules have a smooth and uniform surface. In bulk, the granular blend is free flowing.

58. Although of a crystalline structure, thus closer to that of Pyridoxine, the granules have a size and shape very different from those of Pyridoxine HCl, let alone those of Doxylamine particles.

59. At a macroscopic level, we could also observe that the granules resulting from the roller compaction of ingredients would not stick to plastic, such as polyethylene bags lining the storage drums.

60. In total, to the best of my memory, it took several months of experimentation with time required for assays (such as content uniformity) before being able to produce a uniform blend of powdered Pyridoxine HCl and Doxylamine succinate, which is a long time in our industry to simply uniformly dry mix two powders.

61. The results of the above-mentioned testing were not published or otherwise publicly disclosed by us prior to the filing of a first patent application on the present invention.

III. GENERAL VIEWS ABOUT ROLLER COMPACTION

62. I note that although roller compaction is increasingly used and studied nowadays, at the time of our making the invention behind the patent application No. US 10/670,907, I was aware of many persons in the pharmaceutical industry who thought that roller compaction in general would not work, and who would have preferred the widely used wet granulation method, which according to their school of thought, allows agglomeration of materials.

63. Still today, to the best of my estimation, it appears that up to 80% of the industrial pharmaceutical processes do not use roller compaction.

IV. CONCLUSION

64. The manufacturing method as defined in the amended claims of application No. US 10/670,907 resulted from a relatively long and non-standard work by the inventors on the powders of Pyridoxine HCl and Doxylamine succinate, which would not uniformly mix when dry blended, whatever the method used and even when diluted with excipients.

65. The underlying technical problems solved by the present invention were not known or suggested, in publications or otherwise, prior to the inventors work on these aspects.

66. The roller compactor was also not known or suggested to be used for eliminating the loss of an active ingredient relative to another during a manufacturing process.

67. The use of the roller compactor in a manufacturing process to produce pharmaceutical dosage forms comprising Pyridoxine HCl and Doxylamine succinate as active ingredients surprisingly resulted in dramatic reduction in the relative loss of the Pyridoxine active in comparison with the previously used process. This allowed the new method to substantially exclude the use of an overage of an active ingredient to compensate for potential loss, which confers a clear economical and industrial advantage.

68. The roller compactor method also unexpectedly and advantageously resulted in granules meeting the FDA content uniformity requirements in terms of active ingredients (with a RSD of below about 4%).

69. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

June 25th 2008.
Date

Mr. Victor H. Shulman, Dip.Pharm
M.R.Pharm.S. (UK)

Exhibit A

VICTOR SHULMAN

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EDUCATION

DIPLOMA IN PHARMACY (Equivalent to B.Pharm.)
Witwatersrand School of Pharmacy, Johannesburg South Africa.
Major: Chemistry, Physiology, Pharmacology, Dispensing, Pharmaceutics, Pharmaceutical Forensic Law.
DIPLOMA IN PRODUCTION MANAGEMENT (DISTINCTION)
Damelin Management College, Johannesburg South Africa.
Majors: Production Methodology, break-even Analysis, Forecasting, Preventive Maintenance, Problem Solving Techniques.

PROFESSIONAL ASSOCIATIONS

- Registered Pharmaceutical Chemist (MRPharms.)
- Member of the Royal Pharmaceutical Society of Great Britain.
- Industrial Member of the Canadian Pharmacists Association.
- Member of Skate Canada – Central Ontario (Event Management)

PROFESSIONAL SKILLS

- 40 years of varied experience in the Pharmaceutical Industry.
- Solid management and administrative experience.
- Excellent Mechanical Aptitude.
- Excellent Problem Solving Skills - ability to manage multiple tasks in a pressured environment.
- Strong knowledge of Pharmaceutical Formulation to produce cost effective dosage forms.
- Excellent knowledge and hands on experience in Roller Compaction and formulation of Solid Dose Products by Dry Granulation.
- Leadership by example and Strong Team Player.
- Excellent presentation skills.

COMMUNICATIONS

- Wrote Master Documents and developed multimedia Standard Operating Procedures that were presented to Technicians.
- Published Roll Compaction System cuts changeover time and increases productivity by up to 75% -(Chemical Processing July 1987)
- Developed and delivered Multimedia Training Courses in Basic Pharmaceutics for Operators.

COMPUTER SKILLS

- Windows XP, Microsoft Word, Excel, PowerPoint, Adobe Photoshop, Lotus Organizer, Corel Draw, Adobe Writer, Quark Express.

(1998 – Present)
EMPLOYMENT HISTORY.

(See end of Resume)

1998 Jan-Dec.

DIRECTOR OF PRODUCTION & TECHNICAL SERVICES
Novartis Pharmaceuticals Canada Inc. ***(Caretaker role)***
111 Consumers Drive, Whitby ON. L1N 5Z5

- Merged then managed the Production and Technical Services Department into one unit.
- Trained Production Technicians in preparation for an FDA Pre-Approval Inspection. Successfully completed with compliance being granted in February 1999 for Tablet and Liquid Production.
- Managed a staff of 250 through 4 Managers.

1995-1997

DIRECTOR FOR GMP COMPLIANCE & TRAINING
Apotex Inc., 150 Signet Drive, Weston, ON. M9L 1T9

- Led a steering committee to establish the parameters required to obtain FDA compliance at the existing manufacturing site.
- Developed training modules in Basic Pharmaceutics for operator training.
- Developed a Tablet Tooling Maintenance Department for tooling inspection, cleaning, maintenance and measurement
- Introduced aqueous ultrasonic cleaning methods for cleaning punches and dies - wrote all SOP's, implemented the training and commissioning of the department.
- Re-designed all tablet tooling to enhance product elegance and eliminate production problems from poor tooling design.
- Implemented the DROPS program - Document Reduction and Optimization of Manufacturing Processes in conjunction with Decision Management Consulting.

1984-1995

DIRECTOR OF MANUFACTURING (Shareholder)
Apotex Inc. 150 Signet Drive, Weston, ON. M9L 1T9.

- Commenced employment as Production Manager responsible for all manufacturing and packaging.
- Included scheduling, documentation creation, production administration, Validation and compliance with the GMP's.
- Formulation development, scale up from pilot to manufacturing batch sizes, troubleshooting, method study and improvement.
- Eliminated wet granulation and replaced this with dry granulation using roller compactors.
- Initiated particle size studies and introduced particle size characterization and optimization specifications.
- Converted a 66 Inch Acella Cota originally used to produce M & M's to produce Aqueous Film Coated Tablets.
- Had input into the purchase of equipment such as Tablet Presses, Encapsulating machines and Roller Compactors.
- Performed troubleshooting on marginal products and effected corrections with required validation being performed.
- Set up the APO Master System for electronic document production.

1984-1995 (Continued)

- Initiated an aqueous ultrasonic system for cleaning tooling.
- Implemented a tooling measuring and tracking system to assure integrity of tooling.

1981-1984

TECHNICAL SERVICES MANAGER
Sterling Drug Ltd. Aurora ON

- Problem solved and trouble shooting in the solid dosage parenteral and OTC areas.
- Reformulated marginal products to more cost effective formulations that ran on high speed machinery.
- Scaled up pilot batches from R&D to plant sized batches.
- Eliminated wet granulation in favour of directly compressible formulae.
- Reformulated liquid and ointment products from tanks to sweep kettle methodology.
- Validated reformulated products and all solid dosage products.

1980-1984

PRODUCTION MANAGER - (with option to buy shares)
PHOTRA Ltd. Markam ON.

- Spent 3 years in the colour separation and photo lithography industry with a view to going into my own business.
- Preferred Pharmaceutical production to the printing industry.

1975-1980

PRODUCTION MANAGER
Novopharm Ltd. 1290 Ellesmere Road Scarborough ON

- Commenced employment in Canada as a Production Manager responsible for all manufacturing and packaging.
- Included scheduling, planning, documentation creation, production administration, equipment procurement and the general duties of a Production Manager.
- Managed a staff of 120 through 4 Supervisors.
- Commissioned a side vented coating pan - The O'Hara Pan.
- Purchased and commissioned a roller compactor for the densification of materials prior to encapsulation.
- Purchased and commissioned a new rotary capsule filling machine - the first MG 2 machine in Canada.
- Purchased and commissioned a Gemco double cone blender with an automated loading and unloading platform.

Oct 1975

- **IMMIGRATED TO CANADA FROM SOUTH AFRICA**

1967-1975

- **PRODUCTION MANAGER**

Adcock Ingram / Saphar Laboratories / Rio Ethicals Johannesburg South Africa.

- Began my career in the Pharmaceutical Industry as a Production Pharmacist - responsible for checking all weights and all ingredients into a batch as required by law.
- Promoted to Production Manager and led the manufacturing department through a series of mergers and acquisitions.

1967-1975 (Continued)

SPECIAL PROJECTS - Adcock Ingram 3rd party manufactured in South Africa for many brand name companies such as Ciba, Geigy, Sandoz, Hofmann La Roche, GD Searle, AH Robins, Astra, Alcon, Merck, Willows Francis & Boots (UK)

- Set up a central dispensary - a new innovation in those days.
- Set up an in house print shop to print all labels and inserts.
- Built commissioned and validated an Ethylene Oxide Sterilize that used 15% Ethylene Oxide in Carbon Dioxide as a sterilizing agent. This sterilizer was used for 20 years to sterilize ampoules, metal tubes, dental cartridges, prior to aseptic filling.
- Improved ampoule and cartridge production yields from 65% to 80%.

FROM 1998 To Present.

- Currently Executive of Quality Assurance in charge of Quality for Promising Health Incorporated in Markham
- Currently lecturing in Basic Pharmaceutics at The Academy of Applied Pharmaceutical Sciences.
- Currently training Health Canada (HPBFBI) inspectors in Basic Pharmaceutics through The Academy of Applied Pharmaceutical Sciences.
- Currently lecturing in Basic Pharmaceutics at Seneca College - (School of Biological Sciences and Applied Chemistry) in both their postgraduate and continuing education courses.
- Working as an independent consultant under the company name Darvic Consulting Inc. specializing in formulations. Formulating capsules, tablets and coated tablets for the Pharmaceutical and Nutraceutical industries.
- Strong practical "hands-on" experience in the field of roller compaction for dry granulations.
- Consult and advise on the acquisition of machinery for all aspects of production and packaging.
- Currently also providing GMP training to operators and technicians to prepare them for work in the pharmaceutical industry teaching Basic Pharmaceutics at corporate manufacturing sites.
- References available upon request.